matrices based on hyaluronic acid or derivatives of this molecules, such as Hyaff®, mimic the embryonic hyluronic acid-rich environment and when used as a delivery vehicle for cell-based therapies in adult organisms, promote a recapitulation of these embryonic events. This results in the activation of anabolic factors which induce the differentiation of the cells with the final aim of facilitating tissue repair. The ability of the hyaluronan-based scaffold to reduce also the expression and production of molecules involved in cartilage degenerative diseases indicates its possible use to treat early lesions in osteoarthritic patients. But the problem have to be analyzed also from the clinical point of view. Few clinical studies present the results of autologous chondrocyte transplantation utilize in large degenerative osteoarthritis cartilage lesions.33,34 Although Minas33 reports 90% of patients satisfaction after treatment of large osteoarthritis lesions, the failure rate in this patient group in higher respect to focal lesions (17% and 10% respectively) and 55% of failures occurred in osteoarthritis group. Our experience in very similar: although we found high rate of clinical improvement, the outcome of patients affected by osteoarthritis is lower respect to the focal lesions and most of failures are concentrated in this group. The important finding of our study is that tissue regeneration was found even when implants were placed in joints that had already progressed to osteoarthritis. This findings, combined with results of in vitro studies can address us to suppose that low clinical success of tissue engineered cartilage implants can be connected mostly to mechanical problems. The clinical utilize of existing tissue engineered grafts in osteoarthritis still presents some unresolved problems. First, chondrocyte therapy is suitable for cartilage defects surrounded by healthy cartilage. In osteoarthritis, However, an entire compartment is damaged: the implant placed in the defect will be surrounded by damaged cartilage. The cytokines produced by the chondrocytes around the implant might cause dedifferentiation or apoptosis of the implanted cells. Also the absence of healthy cartilage shoulder can lead to the mechanical damage or mobilization of the implant. Some authors reports good clinical results of combination of autologous chondrocyte implantation with autologous osteochondral plugs.34 Another important issue is represented by mechanical overloading of affected knee compartment even in early osteoarthritis. For this reason we cannot recommend the utilize of existing autologous chondrocyte implants for the treatment of osteoarthritis. For our opinion, the tissue engineered cartilage implant based on hyaluronic acid scaffold can be promising for the treatment of early osteoarthritis, but the mechanical properties of the graft and the mechanical e and biochemical environment of the joint have to be improved. Actually our group is involved in European Project STEPS which aims to solve this issues regarding the possibility to use tissue engineered cartilage in the osteoarthritis joint.

10.2

Manipulation of endogenous healing beyond microfracture...

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In spite of the recent interest in assessing treatments for chondral defects, efforts have been underway for over 250 years to heal articular cartilage with only moderate progress. One must keep in mind that articular cartilage is a highly specialized tissue that needs an intact structure to perform its biochemical, biomechanical and physiological functions. Once the cartilage is damaged, the repair process is typically inadequate, leading to loss of joint integrity, more cartilage damage and more severe joint disease. Various therapies have attempted to improve resurfacing of cartilage defects including surgical modulation relying on endogenous cell repair (full-thickness curettage, spongialization, subchondral bone drilling, subchondral bone plate microfracture, and abrasion arthroplasty), grafting procedures (periosteal autografts, osteochondral graft, sternal cartilage autograft) and chondrocytes transplantation, relying on exogenous cell sources to promote healing.1 So far, no single treatment has clearly shown favorable results in all clinical situations long-term. However, arthroscopic subchondral bone plate microfracture (ASBPM) provides an economic, technically easy procedure that provides good repair tissue in many acute chondral defects without compromising the ability to subsequently perform other surgical techniques.

Arthroscopic subchondral bone plate microfracture was developed, studied and first used clinically by J Richard Steadman, MD to enhance chondral resurfacing in human patients. In humans the procedure typically involves use of an arthroscopic shaver to do a rough shave that removes any cartilage remnants, hand-held curettes to assure removal of the calcified cartilage layer, and surgical awls to make numerous perforations through the subchondral bone plate. The procedure has been used in about 3,000 humans over the past 18 years. In a study2 evaluating human patients 7 to 17 years after microfracture, 80% experienced a decrease in pain and improvement in daily living. Significant improvement was recorded for the Lysholm function score and the Tegner activity scale. There was also significant improvement in the SF-36 and WOMAC scores. These clinical successes have led to experimental work assessing the degree of improvement in placebo controlled studies. In 1996 a full thickness chondral defect model was developed on the medial condyle of horses to assess the improvement seen with ASBPM compared to non-ASBPM treated defects.3 The model was carried out in the horse to allow the use of routine arthroscopic equipment, access to cartilage with similar thickness to that of humans on the medial femoral condyle and the ability to subject the horse to controlled long-term strenuous exercise as well as this lesion being a clinical entity in the athletic horse. The goal of this study was to gain better understanding of how ASBPM may augment the healing processes using clinical, gross, histologic, and biochemical examinations. This study demonstrated that a significant increase in repair tissue was seen in defects treated with ASBPM compared to untreated defects and that there was an increase in type II collagen. It was surprising that the histologic character of the repair tissue was similar when both groups were compared. The character of the repair tissue was a mixture mainly of fibrocartilage. These data were also later confirmed in experimental models in dogs and rabbits as well.4,5 The equine study also suggested that many of the events that led to differences between the ASBPM and non-ASBPM treated defects occurred prior to 4 months. This finding led to a follow-up study that evaluated the short-term effects of ASBPM treatment at the molecular level assessing tissues at 2 week intervals up to 8 weeks.6 This study reconfirmed an up-regulation of type II collagen with ASBPM when compared to non-ASBPM treated defects as well as the increased volume of tissue that histologically was not different. During model development it was observed that using a motorized shaver for debridement of partial thickness lesions may be retaining calcified cartilage. Likewise areas with calcified cartilage retained in the first two equine studies subjectively had poor attachment of the repair tissue to surrounding bone or cartilage. To confirm the consequences associated with incomplete debridement of the calcified cartilage, another controlled study was undertaken which specifically compared the presence or absence of calcified cartilage on defect healing with ASBPM, as well as, arthroscopic biopsy on long-term repair tissue healing.7

The results of this study demonstrated a greater volume of repair tissue with the removal of calcified cartilage. A significant negative correlation to presence of calcified cartilage and repair tissue attachment was also observed. No long-term adverse effects were noted with the arthroscopic biopsy of defects. Similar to other studies no significant difference in histologic repair tissue character

was noted between the treatment groups. It was concluded that the removal of the calcified cartilage layer appears to provide an optimal amount and attachment of repair tissue and that close arthroscopic visualization is recommended for debridement of clinical lesions to ensure complete removal of the calcified cartilage layer. While it has been shown that ASBPM has a significant beneficial effect on improving repair tissue volume and type II collagen content of chondral defects, improvement in the character of the repair tissue especially as it relates to biochemical and histologic nature is still an objective. In fact most of the recent work with ASBPM has focused on methods to make such improvements. Aimed at such improvement and based on the major role that both insulin-like growth factor-1 (IGF-1) and interleukin-1 receptor antagonist (IL-1Ra) play in anabolic metabolism of articular cartilage and anti-inflammatory control of diseased joints respectively, these molecules were the focus of recent ASBPM studies. Briefly, an in vitro experimental study combined these two molecules to demonstrate a significant increase in restoration of proteoglycan content in IL-1 depleted cartilage.8 Based on these positive data an in vivo study was carried out in horses.9 To preserve the benefits of the overall ASBPM procedure, the arthroscopic template and ease of ASBPM, these two molecules were delivered to the joint using a single intraarticular injection containing adenoviral vectors with equine IGF-1 and IL-1Ra as transgenes. This effectively allowed these two molecules to be simultaneously produced by the synoviocytes within the joint. The results of this study were successful in further increasing Type II collagen content as well as improving the concentration of proteoglycan significantly in the repair tissues exposed to IGF-1/IL-1Ra. Furthermore, there were no detrimental effects seen with this augmentation of ASBPM alone. Others have also assessed the ability to augment the character of repair tissue following ASBPM although to date these methods have been performed using arthrotomy incisions.

Breinan et al. reported on a canine model of cartilage healing where ASBPM was augmented with a type II collagen matrix.4 This technique dictated the use of an open incision as well as suturing the collagen matrix to the surrounding articular cartilage. The results of this study did not demonstrate any significant improvement in tissue character, above the fibrocartilagenous repair tissue normally observed subsequent to ASBPM alone. Dorotka et. al. assessed the treatment of experimental ovine cartilage defects with ASBPM alone, ASBPM with a 3-D collagen matrix as well as ASBPM with the 3-D matrix containing autologous chondrocytes.10 Delivery of the matrix again mandated an arthrotomy incision and fixation using sutures to the surrounding articular cartilage. The group treated with matrix plus chondrocytes was observed to have repair tissue having the greatest hyaline-like component although evidence of statistical comparisons to ASBPM alone was not made. Based on subjective scores there was improvement in the O'Driscoll score when ASBPM plus matrix alone was compared to matrix with chondrocytes, however, neither of these groups were significantly better than ASBPM alone. Thus, the addition of matrix containing chondrocytes did not definitively show improvement to ASBPM alone. To assess if a more stable clot at the time of debridement would improve healing after ASBPM Hoemann et. al. also used an ovine experimental model.11 All defects were subjected to ASBPM, the control limb received no further treatment while the treated limb had the defect filled using a mixture of chitosan-glycerol and autologous blood, which was then allowed to clot in the defects. While the authors elected to perform an open incision all described procedures would theoretically be possible arthroscopically. Four animals were sacrificed immediately post-operatively to assess if more clot was retained with chitosan-glycerol/blood treatment. While numerically the chitosan-glycerol/blood treated defects had greater coverage the comparison to ASBPM alone was not reported to be statistically different. The gross and histologic results of this study were encouraging with treated defects showing greater repair tissue with a more hyaline-like nature. Furthermore, two of the six ICRS histologic grading criteria (smoothness and cell organization) were significantly improved in the chitosan-glycerol/blood compared to untreated defects (ASBPM alone). It should be noted this was a short-term study of four months duration and only four of fourteen condylar defects did not develop subchondral bone cysts by the termination of the study. The results of this study support further work to assess long-term outcomes as well as the potential for other methods of defect filling at the time of surgery plus or minus a cellular component to improve repair tissue quality. Based on the ability of bone morphogenetic protein 7 (BMP-7) to induce chondrogenesis Kuo et. al conducted an experimental study in juvenile rabbits to assess the ability of BMP-7 to improve the repair tissue following ASBPM.5 While the surgical technique did not use awls commercially produced for microfracture the addition of BMP-7 impregnated in a type I collagen sponge significantly increased the repair tissue matrix and cellular organization based on ICRS histologic outcome parameters. The addition of BMP-7 impregnated in a type I collagen sponge significantly increased the repair tissue matrix and cellular organization based on ICRS histologic outcome parameters. It is important to note this study was carried out in young rabbits for a short duration but was well controlled. Also noteworthy was the fact the collagen sponge was press fitted into one microfracture hole which could lend its self to arthroscopic application. While defects treated with BMP-7 and ASBPM were not completely filled with repair tissue, nor did they have normal hyaline tissue, the results clearly support this treatment modality being tested in a large animal model with long-term follow-up. The routine use of ASBPM in both human and veterinary practice is wide spread and remains the treatment of choice for resurfacing acute chondral defects by many surgeons. It is well realized that the repair tissue obtained subsequent to this procedure is characterized by fibrocartilage but appears to be functional long-term in many cases. Even with this already successful procedure the medical community strives for enhancement of this procedure to gain a more hyaline repair tissue with characteristics closer to native articular cartilage. Since the focused experimental work began in 1996 it appears that altering the joint environment through the use of anabolic and anti-inflammatory molecules as well as augmenting the defect bed with an arthroscopically delivered cellular matrix may be the next step beyond microfracture...

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